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Uveitis, the Most Faithful Partner of Axial Spondyloarthritis

Citera G, Schneeberger EE, Cavalieri M, Campusano RR, Orozco MC, Sommerfleck FA, Zamora N and Capelusnik D*

Department of Rheumatology, Institute of Psychophysical Rehabilitation, Argentina

Abstract

Introduction: The objective of this study was to determine the prevalence of AAU in a cohort of patients with axSpA and to describe their clinical characteristics, frequency of episodes, response to treatment and long-term prognosis, as well as, their association with general disease characteristics.

Material and Methods: A longitudinal study was carried out. We included patients that fulfilled the ASAS criteria for axSpA (ASAS 2009 criteria) from ESPAXIA (Estudio de eSPondiloartritis Axial Irep Argentina) cohort. Sociodemographic data, type of axSpA, extra-articular manifestations, comorbidities, disease duration and treatments received numbers of episodes of uveitis, incidence date, and its characteristics, treatment and complications were consigned. Morning stiffness, night pain, global pain and patient's and physician's global assessment (NVS), number of swollen joints (44), axial mobility (BASMI), enthesitis (MASES), ESR, CRP and *HLA-B27* were registered. BASDAI, BASFI and ASQoL self-questionnaires were administered.

Results: Two hundred and thirty one patients with axSpA were included, 174 male (75.3%) with a median age of 46 years (IQR 36 to 57) and median disease duration of 20.5 years (IQR 10.5 to 30.5). Sixty patients (26%) had at least one episode of uveitis, being the first manifestation of the disease in 22 of them (37.9%). Acute anterior uveitis was the most frequent form, and it was observed in 59 patients (98.3%). The mean number of episodes was 4.78 (SD 5.64). Recurrences were unilateral in 48.8% of cases. The treatment received was local in 42 (79.2%) of the patients. Twenty patients (33.33%) where in treatment with Tumor Necrosis Factor α inhibitors (TNFi) by the time of the data collection: 17 patients with monoclonal antibodies and 3 with Etanercept (ETN). Patients with axSpA and UAA received monoclonal agents more frequently (85% *vs.* 15%, p=0.018). The presence of UAA was associated with a lower survival of biological medication, with a median of 91.42 months (SD 19.74) *vs.* 109.44 months (SD 12.34). Twelve patients (22.2%) presented a complication after the first episode, being the decrease in visual acuity and cataracts, the most frequent ones (16.7% and 5.6%, respectively). The presence of uveitis was significantly associated with longer disease duration ($\bar{x}$ 24.9 years *vs.* $\bar{x}$ 20.7 years, p=0.038) and with the presence of *HLA-B27*, (69% *vs.* 47.4%, p=0.006) and these associations were maintained in the multivariate analysis, after adjusting for other variables.

Conclusion: The prevalence of uveitis in our cohort was 26%, and it was significantly more frequent in patients *HLA-B27* (+) and with longer disease duration.

Keywords: Uveitis; Spondyloarthritis; Axial spa; *HLA-B27*

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Correspondence:
Citera G, Department of Rheumatology, Institute of Psychophysical Rehabilitation, Argentina; E-mail: gustavocitera@gmail.com

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Introduction

Axial Spondyloarthritis (axSpA) consists in a group of heterogeneous chronic inflammatory diseases with common clinical, serological and genetic characteristics such as the absence of the rheumatoid factor and the high frequency of the *HLA-B27* antigen [1]. These diseases include: Ankylosing Spondylitis (AS), Reactive Arthritis (ReA), Psoriatic Arthritis (PsA), arthritis associated with Inflammatory Bowel Disease (IBD) and juvenile axSpA [2].

This group of conditions may also have extra-articular involvement, being the uveitis, skin involvement and intestinal inflammation the most frequently found, but also compromise of the heart, lung and kidneys can be detected in these patients [3].

Acute Anterior Uveitis (AAU) is the acute inflammation of the anterior segment of the eye, also called iritis or iridocyclitis. It is characterized by an episode of sudden onset, which usually lasts

less than three months, with a good prognosis and rapid response to local anti-inflammatories and mydriatics drugs. The clinical picture is characterized by pain, photophobia, epiphora, ocular redness, and in more severe cases, blurred vision due to abundant inflammatory precipitates in the anterior chamber of the eye. In most cases it is unilateral, but with a marked tendency to relapse with alternating affectation of both eyes, being able in those cases to leave secular damage [4].

Its prevalence is estimated at 38 to 150 per 100,000 inhabitants per year in Western countries [5]. AAU can be idiopathic when it occurs in isolation and with no apparent known cause, but it can also be associated with systemic diseases, such as Spondyloarthritis (SpA), Behçet's disease, Juvenile Idiopathic Arthritis (JIA) and sarcoidosis [6].

The AAU and SpA share the genetic predisposition related to positivity for *HLA-B27* [6,7]. Also, uveitis represents the most frequent extra-articular manifestation of axSpA, with a global prevalence of around 32.7% [8]. Its frequency is higher in patients with AS, probably due to its stronger association with *HLA-B27* + and lower in PsA, ranging from 2% to 25%. In this case, its form of presentation is usually more insidious, chronic, bilateral and active [9]. The AAU is observed in 25% in the axSpA associated with IBD, and in about half of the cases it precedes both the intestinal and articular manifestations [10].

Last reports from the COMOSPA cohort, reported a prevalence of AAU of 20.3%, and lower if only Latin America patients were evaluated, with 15.8% [11].

In Argentina, RESPONDIA cohort reported a prevalence of AAU of 10% in SpA in general, but 46.7% of the patients had PsA [12]. However, it is important to add that the design of this study was retrospective; hence the UAA data was collected through the revision of patients' medical records.

The objectives of this study were to determine the prevalence of AAU in a cohort of patients with axSpA. Also, we described the characteristics and frequency of the episodes, response to treatment and long-term prognosis. Furthermore, we studied their relationship with clinical variables of the disease.

Material and Methods

A longitudinal study was carried out, including patients that fulfilled the ASAS criteria for axSpA (ASAS 2009) from the prospective longitudinal cohort ESPAXIA (*Estudio de Espondiloartritis Axial IREP Argentina, meaning: IREP Argentina´s Axial Spondyloarthritis Study*) [13].

Data was collected during the annual control visits of the cohort from patients included from January 2008 to July 2017. The presence of uveitis was collected based on cases reported by patients during their visit and by telephone interview in case there had been additional information to collect.

Sociodemographic data, such as age, sex, family background, employment status; disease characteristics, type of axSpA (AS or axSpA non-radiographic-nr-axSpA), axSpA form (AS, juvenile axSpA, undifferentiated axSpA, PsA, axSpA associated with IBD and ReA), presence of extra-articular manifestations, comorbidities, disease duration at last follow-up visit and treatments received were recorded. The history of AAU episodes, quantity, onset date and clinical characteristics, treatments received and sequelae were documented. On physical examination we evaluated morning stiffness, measures of axial mobility by Bath Ankylosing Spondylitis Metrological Index (BASMI), number of swollen joints (44) and enthesitis sites by Maastricht AS Enthesitis Score (MASES) [14,15]. The Numerical Visual Scale (NVS) was used to evaluate pain, night pain, global assessment of disease activity according to the patient and the physician. Disease activity was determined through the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) functional capacity by Bath Ankylosing Spondylitis Functional Index (BASFI) [16], and quality of life with Ankylosing Spondylitis Quality of Life (ASQoL) [17]. The Simplified Ankylosing Spondylitis Disease Activity Score (SASDAS) ESR/CRP indexes were also calculated [18].

Table 1: Sociodemographic variables and characteristics of axSpA.

	axSpA (n=231)
Age m (RIC)	46 (36-57)
Male Sex n (%)	174 (75.3)
Disease duration (years) m (IQR)	20.5 (10.5-30.5)
Family history of axSpA n (%)	101 (43.7)
HLA-B27 positive n (%)	99/121 (81.8)
Main Diagnosis	
AS	162 (70.7)
PsA	19 (8.3)
axSpA associated with IBD	7 (3.1)
ReA	4 (1.7)
nr-axSpA	5 (2.2)
Juvenile SpA	32 (14)
Treatment	
NSAIDs n (%)	218 (94.3)
Sistemic steroids n (%)	131 (56.7)
cDMARDs n (%)	93 (40.6)
Biological therapy n (%)	53 (22.9)

axSpA: axial Spondyloarthritis; AS: Ankylosing Spondylitis; PsA: Psoriatic Arthritis; IBD: Inflammatory Bowel Disease; ReA: Reactive Arthritis; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; cDMARDs: conventional Disease-Modifying Antirheumatic Drugs

This study was reviewed and approved by the Ethics Committee of Instituto de Rehabilitación Psicofísica.

Statistical analysis

Descriptive statistics was performed. The categorical variables were expressed in frequency and percentage and the continuous variables in median (*m*) and Inter Quartile Range (IQR). The categorical variables were compared with the Chi^2 test and Fisher's exact test and for the continuous variables with student's T test. Multiple logistic regression analysis was used to identify associated variables, using the presence of uveitis as the dependent variable. Those variables with a p value less than 0.1 in the univariate analysis were entered as independent in the multivariate model, as well as different variables selected at researcher's discretion. A value of $p<0.05$ was considered significant. Statistical package SPSS version 10.0 was used for the analysis.

Results

Two hundred and thirty one patients were included, of which 174

Table 2: Comparison of sociodemographic, clinical and therapeutic variables of axSpA between patients with and without history of AAU.

	Group UAA (n=60)	Group no UAA (n=171)	p
Age $\bar{\bar{X}}$ (SD)	49.8	47.1	0.194
Male n (%)	43 (71.7)	131 (76.6)	0.487
Family history of axSpA n (%)	25 (41.7)	76 (44.4)	0.763
***HLA-B27* positive n (%)**	**40 (69)**	**81 (47.7)**	**0.006**
Disease duration (years) $\bar{\bar{X}}$ (SD)	**24.9 (14.2)**	**20.7 (13.2)**	**0.038**
Diagnosis delay (years) $\bar{\bar{X}}$ (SD)	7.5 (9.7)	6.1 (7.6)	0.27
Comorbidities n (%)	55 (93.2)	165 (96.5)	0.284
EAMs n (%)	51 (86.4)	143 (83.6)	0.682
Psoriasis n (%)	3 (5.1)	12 (7)	0.765
Tendonitis n (%)	1 (1.7)	1 (0.6)	0.443
Tarsitis n (%)	8 (13.8)	18 (10.5)	0.481
Dactylitis n (%)	3 (5.2)	8 (4.7)	1
Enthesitis n (%)	11 (18.6)	20 (11.7)	0.189
Schober's test $\bar{\bar{X}}$ (SD)	2.7 (1.5)	2.9 (1.7)	0.332
MASES $\bar{\bar{X}}$ (SD)	1.8 (2.8)	1.4 (2.6)	0.262
ASQoL $\bar{\bar{X}}$ (SD)	6.1 (5.1)	6 (5.2)	0.938
BASFI $\bar{\bar{X}}$ (SD)	4.1 (3.1)	3.9 (2.8)	0.539
BASRI $\bar{\bar{X}}$ (SD)	3.5 (4)	6.6 (5.2)	0.029
mSASSS $\bar{\bar{X}}$ (SD)	19.5 (21.7)	24.6 (24.7)	0.554
Treatment			
NSAIDs n (%)	57 (98.3)	161 (94.2)	0.298
cDMARDs n (%)	32 (55.2)	61 (35.7)	0.013
Biological therapy n (%)	17 (29.3)	36 (21.1)	0.21
Sistemic steroids n (%)	99 (57.9)	32 (55.2)	0.76

axSpA: axial Spondyloarthritis; AAU: Acute Anterior Uveitis; EAMs: Extra-Articular Manifestations; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; ASQoL: Ankylosing Spondylitis Quality of Life; BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiology Index; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAIDs: Nonsteroidal Antiinflamatory Drugs; cDMARDs: conventional Disease-Modifying Antirheumatic Drugs

were male (75.3%). The median age was 46 years (IQR 36 to 57) and the median disease duration at the last recorded follow up visit was 20.5 years (IQR 10.5 to 30.5). Other characteristics of the population are shown in Table 1.

Sixty patients (26%, 95% CI 20.3 to 31.7) presented at least one episode of uveitis, being the disease first manifestation in 22 patients (37.9%). In other words, 9.5% of the axSpA initiated the disease with the eye involvement. From the total of patients with uveitis, 42 (70%) has the diagnosis of AS, followed by 6 (10%) with juvenile axSpA, 7 PsA (11.6%), 3 axSpA associated with IBD (5%), 1 ReA (1.7%) and 1 nr-axSpA (1.7%). Almost all patients 59/60 (98.3%) had AAU, being the remaining one, a panuveitis. The average number of episodes per patient was 4.78 (SD: 5.64). Seventeen patients had 1 episode, 15 patients: 2 episodes, 8 patients: 3 episodes and 20 patients: 4 or more episodes. In 48.8% of cases, recurrences were unilateral, that is to say, in the same eye. The median duration of each event decreased with each relapsing episode [1st event *m* 30 days (IQR 14.5 to 60.5), 2nd *m* 21 days (IQR 7 to 48.7), 3rd *m* 20.5 days (IQR 7 to 39), 4th *m* 18 days (IQR 9 to 39) and the last event *m* 22.5 days (IQR 9 to 45)]. Although it was numerically shorter, did not reach statistical significance. The

Table 3: Characteristics associated with the presence of AAU. Multiple logistic regressions.

				95% CI	
	B	Sig.	OR	Lower	Upper
Age at onset	-0.010	0.530	0.990	0.960	1.021
Male sex	-0.405	0.274	0.667	0.323	1.377
Main diagnosis	-0.042	0.599	0.959	0.821	1.120
Disease duration	**0.027**	**0.033**	**1.027**	**1.002**	**1.053**
***HLA-B27* positive**	**0.997**	**0.003**	**2.710**	**1.412**	**5.202**

Dependent variable: AAU

treatment received was local in 42 (79.2%) of the patients. Twelve patients (22.2%) presented sequelae after the first episode, being the most frequent the decrease in visual acuity and cataracts (16.7% and 5.6%, respectively). The sequels after the last episode in patients with more than one, or the only one, in patients with one episode was, in descending order of frequency: visual acuity decrease (58.8%), synechia (29.4%) precorneal precipitates (29.4%), cataracts (23.5%) and corneal ulcers (11.8%). The prevalence of complications increased proportionally as the number of episodes of AAU (1 episode: 22.2% reported sequelae, 2 episodes: 37.5%, 3 episodes: 39.3%, 4 episodes: 55.6% and >4 episodes: 76.5%). The patient who had panuveitis resolved without sequelae.

When comparing the sociodemographic, clinical and therapeutic characteristics, patients with axSpA who presented AAU had a longer disease duration $\bar{x}$ 24.9 ± 14.2 years *vs.* $\bar{x}$ 20.7 ± 13.2 years, p=0.038) and higher frequency of positivity for *HLA-B27* (69% *vs.* 47.4%, p=0.006). Nevertheless, no difference was observed in the remaining variables between both groups Table 2. In the multivariate analysis, longer disease duration (OR: 1.027, 95% CI: 1.002 to 1.053) and presence of *HLA-B27* (OR: 2.710, 95% CI: 1.412 to 5.202) were independently associated with the presence of uveitis Table 3.

In relation to the treatment of the SpA, 55.2% of the patients with AAU received treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs) as part of their treatment, *vs.* 35.7% of patients who did not have AAU (p=0.013). The most frequently used cDMARDs were: Methotrexate (53.5%) followed by Sulfasalazine (43.3%). At the time of data collection at last visit, among the 60 patients with a history of AAU, 20 of them were receiving tumor necrosis factor α inhibitors (TNFi): 12 patients Adalimumab (ADA), 3 Infliximab (IFX), 2 Certolizumab (CTZ) and 3 Etanercept (ETN). Patients with axSpA and AAU received monoclonal TNFi more frequently compared to ETN (85% *vs.* 15%, p=0.018). In association with this, patients with AAU received less frequently cDMARDs, (33% *vs.* 67%, p=0.16).

Discussion

AAU is the axSpA most frequent extra-articular manifestation observed in patients with axSpA, with a prevalence that varies between 14.5% and 37% according to different series [5,11,19]. Recently, a Systematic Literature Review (SLR) that included 1989 patients with axSpA, reported a prevalence of 32.7%, and similar to our results, the AAU was associated with longer disease duration and the presence of *HLA-B27* [20]. However, both factors could be a bias, since ophthalmologist most frequently request *HLA-27* from patients with non-infectious uveitis and in as much as this is a cumulative prevalence it is possible to understand that the longer disease duration, the more likely to have episodes of uveitis. In a meta-

analysis conducted by Stolwijk et al. [21], the prevalence of AAU was 25.8%, and it was also significantly associated with disease duration (17.4% in patients with <10 years of disease duration and 38.5% in those with greater than 20 years). In this study, some variability was observed in the frequency of AAU according to the geographic area, and particularly the prevalence in Latin America was one of the lowest, compared with other regions [21]. In Latin America, there is no enough evidence available regarding this manifestation. The RESPONDIA study, an Ibero-American cohort of spondyloarthritis, reported even a lower frequency of AAU, corresponding to 10% [12]. This result was probably determinate due to the fact that 46.7% of the sample included patients with PsA and only 33.2% had diagnosis of AS, and also due to the uveitis reported was at the discretion of the investigator during the review of the clinical history. Sampaio-Barros et al. [19], reported in the SpA Brazilian population, 12% of prevalence of AAU, with a frequency of 14.5% particularly in AS. More recently, the COMOSPA cohort, published a prevalence of UAA in patients with SpA in Latin America of 15.8%, being Mexico the place with the highest values (23.9%), followed by Argentina (14.9%) and lastly, Colombia (11.8%). Again, it is important to note that this cohort includes patients with SpA instead of axSpA, however, as their data show, almost 85% of the patients evaluated had axial compromise [11].

In our study, similar to other series, the highest frequency of AAU was observed in patients with AS, however when we analyzed the prevalence of AAU between the different types of axSpA, the results were higher for axSpA associated with IBD and PsA. Nevertheless, these data must be interpreted with caution because the number of patients in those groups were too low (<10 in the rest of them).

In our study, similar to other series, the highest frequency of AAU was observed in patients with AS, however a comparison of the AAU frequency between the different types of axSpA could not be made due to the low number of patients (<10) in the rest of them. As previously expressed, the presence of *HLA-B27* in our study, was strongly associated to the presence of AAU, inferring a chance almost three times higher in patients *HLA-B27* positive. Similar results were found in several studies, with Odd Ratios as high as 4.2 (p=0.001) [20,22-24]. Other authors observed association of AAU with greater axial compromise, less mobility [25] and lower functional capacity [26], but these associations were not observed in our study.

Regarding the episodes characteristics and, in agreement with other reports, the most frequent type of uveitis in our cohort was AAU, with a marked tendency towards one-sidedness and predisposition to recurrence, although without predilection for the condition on a same eye [18,19]. The duration of the first episode was considerably longer than the rest of them, and it was decreasing with recurrence. This could be explained because a patient, who has already suffered an episode of uveitis, would be alerted about this condition, and therefore he would consult earlier, with a quick access to specific treatment. However, these data was not confirmed in this study.

In more than a third of the patients, AAU was the disease first manifestation. This data matches with what is described in the literature, in which, cases of ocular involvement are described several years before the axial involvement [27]. Wendling et al. [28], in the DESIR cohort, also reported that AAU preceded the onset of inflammatory back pain in 37% of the cases, while in 45% of them, it occurred after the first musculoskeletal manifestations and in only 18% of cases, ocular and inflammatory back pain involvement was almost simultaneous [28].

The ocular sequelae lesions after the AAU episodes usually occur due to several factors such as: recurrent episodes, delay in diagnosis and delay in beginning the specific treatment. Nevertheless, the prognosis of these patients can be improved with an adequate and timely treatment. On the other hand, we must also bear in mind that corticoid treatment, whether topical or systemic, can also cause injuries at ocular level. In our study, the complications of uveitis were related to the number of recurrences.

The acute attack of the anterior uveitis usually resolves completely with topical glucocorticoids, and less frequently oral corticosteroids or intraocular injections are required [29]. In recurrent attacks of uveitis, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) can relieve symptoms for a short period [30]. cDMARDs such as Sulfasalazine (SSZ) and Methotrexate (MTX) have limited evidence [31,32]. In our study, although we observed a significantly higher frequency of treatment with cDMARDs in patients with AAU, but lamentably we could not discriminate whether the cDMARDs were indicated as part of the treatment for ocular involvement or for any other disease manifestation. Within biological therapies, TNFi, mainly monoclonal agents, have excellent efficacy in the treatment of AAU [33-37]. Most of our patients with AAU were treated with monoclonal TNFi, possibly in conjunction with the aforementioned.

In this current study, the prevalence of family history of axSpA was surprisingly higher than expected; however, AAU was not associated with this finding.

Our study has some limitations. Firstly, some patients had to be interviewed in order to obtain the information that was not included in the data base, and this situation could be subject to memory bias. Secondly, although it is a longitudinal cohort of a single center, the number of patients analyzed was low. Thirdly, the evaluations of the patients were annually, so in the majority of the cases the episodes of AAU did not coincide temporarily with the day of the visit, therefore, the relationship of the uveitis episodes with the disease activity could not be analyzed properly.

In conclusion, in the Argentina ESPAXIA cohort the prevalence of uveitis was 26%, and the presence of AAU was significantly associated with the presence of *HLA-B27* and with longer disease duration.

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